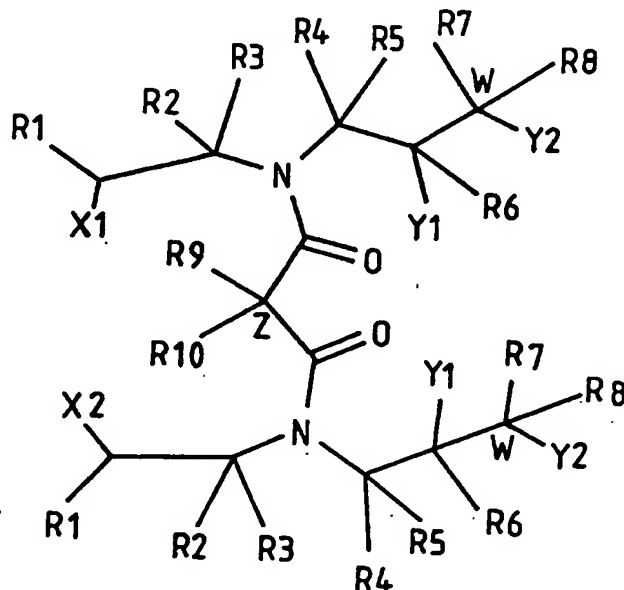




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(21) International Application Number: PCT/GB93/02061 (22) International Filing Date: 4 October 1993 (04.10.93) (30) Priority data: 92309140.9 7 October 1992 (07.10.92) EP (34) Countries for which the regional or international application was filed: AT et al. 93307620.0 27 September 1993 (27.09.93) EP (34) Countries for which the regional or international application was filed: AT et al. (71) Applicant (for all designated States except US): QUEST INTERNATIONAL B.V. [NL/NL]; Huizerstraatweg 28, NL-1411 GP Naarden (NL).		(72) Inventors; and (75) Inventors/Applicants (for US only) : MOTION, Keith, Robert [GB/GB]; 22 Mount Pleasant Close, Lyminge, Kent CT18 8HF (GB). JANOUSEK, Angela [GB/GB]; Juniper House, 5A Woodlawn Way, Canterbury, Kent CT2 7LS (GB). WATKINS, Steven [GB/GB]; 7 Kiln Close, Challock, Ashford, Kent TN25 4DA (GB). (74) Agent: KEITH W. NASH & CO.; Pearl Assurance House, 90-92 Regent Street, Cambridge CB2 1DP (GB). (81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: HYDROXY ALKYL AMIDES OF DICARBOXYLIC ACIDS AND THEIR USE IN COSMETIC COMPOSITIONS



(57) Abstract

A class of pseudoceramide having the formula shown in which: R1 is a hydrocarbon group; R2-R8 are each independently H or CH₃; R9 and R10 are each independently H or hydrocarbon group of up to 24 C atoms; X1 and X2, are independently H or OH; Y1 and Y2 are H or OH, at least one of Y1 and Y2 being OH; wherein the C atom Z, with associated R9 and R10, can be absent; and the C atoms W, with associated R7 and Y2, can be absent, is disclosed. These find use in compositions, particularly cosmetic compositions, suitable for topical application to skin, hair or nails.

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- 1 -

Hydroxy alkyl amides of dicarboxylic acids and their use in cosmetic compositions

Field of the Invention

This invention concerns cosmetic compositions, particularly those including so-called "pseudoceramides", and relates to a novel class of pseudoceramides and their use in the treatment of skin, hair and nails.

Background to the Invention

Ceramides are a group of naturally occurring compounds having the formula shown in Figure 1, where $m = 10-16$ and $n = 12-24$. Ceramides and ceramide derivatives are believed to play an important role in the water permeability properties of the skin, functioning to give increased strength to the skin structure to decrease water loss and so improve the condition of the skin, and it is known to use ceramides and ceramide derivatives as components of skin care compositions.

Certain non-naturally occurring variants of ceramides, known as pseudoceramides, have been synthesised or proposed. Generally these are designed to have certain properties similar to those of ceramides and to mimic the behaviour of ceramides in relation to the skin so as to be usable in skin care compositions as cheaper substitutes in place of naturally occurring skin ceramides.

Known pseudoceramides include those described in EP

- 2 -

0420722 A of L'Oreal and EP 0482860 A of Unilever.

The present invention is based on a novel class of pseudoceramides.

Summary of the Invention

In one aspect the present invention provides compounds of the formula shown in Figure 2, in which:

R1 is a hydrocarbon group;

R2-R8 are each independently H or CH₃;

R9 and R10 are each independently H or a hydrocarbon group of up to 24 carbons;

X1 and X2 are independently H or OH;

Y1 and Y2 are H or OH, at least one of Y1 and Y2 being OH;

wherein the C atom Z, with associated R9 and R10, can be absent; and

the C atoms W, with associated R7 and Y2, can be absent.

Compounds in accordance with the invention have certain properties similar to those of naturally occurring skin ceramides, and can thus be considered to constitute a novel class of pseudoceramides.

The compounds of the invention thus find application in the treatment of skin, hair and nails.

In a further aspect the invention thus provides a composition, particularly a cosmetic composition, suitable for topical application to skin, hair or nails, comprising a compound in accordance with the invention.

The invention also covers use of a compound in accordance

- 3 -

with the invention as an agent for skin water barrier repair, for improving nails and/or for improving hair.

The composition may include one or more compounds in accordance with the invention, conveniently in an amount in the range 0.00001 to 50% by weight, preferably 0.001 to 20% by weight, more preferably 0.1 to 10% by weight, eg 0.8 to 5.0% by weight.

The composition preferably includes a suitable carrier vehicle for the compound. This will generally be a cosmetically acceptable vehicle which acts as a diluent, dispersant or carrier to enable the compound to be dispersed onto the skin, hair or nails and distributed thereon.

Suitable carrier vehicles include water, liquid or solid emollients, solvents, humectants and powders. Examples of these types of vehicles, which can be used singly or as mixtures, are given in EP 0482860 A.

The carrier vehicle will usually form from 10 to 99.9% by weight, preferably from 50 to 90% by weight, of the composition, and can, in the absence of other cosmetic adjuncts, form the balance of the composition.

Optional skin benefit materials and cosmetic adjuncts may also be included.

Compounds in accordance with the invention are found to have excellent emulsifying, gelling and thickening properties and are well suited to use in formulations in the form of viscous emulsions or gels.

- 4 -

A particularly convenient form of the composition according to the invention is an emulsion, in which case an oil or oily material will normally be present, together with an emulsifier (if required) to provide either a water-in-oil emulsion or an oil-in-water emulsion, depending largely on the average hydrophilic-lyophilic balance (HLB) of the emulsifier employed.

The composition according to the invention can optionally comprise one or more oils or other materials having the properties of an oil.

Examples of suitable oils include mineral oil and vegetable oils, and oil materials, such as those already proposed as emollients in EP 0482860 A. Other oils or oily materials include silicone oils, both volatile and non-volatile, such as polydimethyl siloxanes.

The oil or oily material, when present for the purposes of forming an emulsion, will normally form up to 90% by volume, preferably from 10 to 80% by volume, of the composition.

The composition according to the invention can also optionally comprise one or more emulsifiers the choice of which will normally determine whether a water-in-oil or an oil-in-water emulsion is formed.

When a water-in-oil emulsion is required, the chosen emulsifier or emulsifiers should normally have an average HLB value of from 1 to 8. When an oil-in-water emulsion is required, a chosen emulsifier or emulsifiers should have an average HLB value greater than 8.

- 5 -

Examples of suitable emulsifiers are given in EP0482860 A.

It is to be understood that two or more emulsifiers can be employed if desired.

The amount of emulsifier or mixtures thereof to be incorporated in the composition of the invention when appropriate is typically from 1 to 50% by weight, preferably from 2 to 20% by weight, and more preferably from 2 to 10% by weight of the composition.

The composition of the invention can also comprise water, usually up to 98% by volume, preferably from 5 to 80% by volume.

The composition of the invention can also optionally comprise a high molecular weight silicone surfactant which can also act as an emulsifier, in place of or in addition to the optional emulsifier(s) already referred to. The silicone surfactant is typically a high molecular weight polymer of dimethyl polysiloxane with polyoxyethylene and/or polyoxypropylene side chains as disclosed in EP 0482860 A.

The composition may take a variety of forms, eg skin and nail creams and lotions, sun-tan products, soaps, bath oils, lotions and foams, shampoos, hair conditioners etc.

The composition of the invention can, for example, be formulated as a lotion having a viscosity of from 4,000 to 10,000 mPas, a fluid cream having a viscosity of from 10,000 to 20,000 mPas or a cream having a viscosity of from 20,000 to 100,000 mPas or above. The composition can

- 6 -

be packaged in a suitable container to suit its viscosity and intended use by the consumer.

For example, a lotion or fluid cream can be packaged in a bottle or a roll-ball applicator or a propellant-driven aerosol device or a container fitted with a pump suitable for finger operation. When the composition is a cream, it can simply be stored in a non-deformable bottle or squeeze container, such as a tube or a lidded jar.

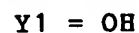
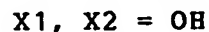
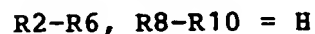
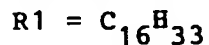
The invention accordingly also provides a closed container containing a composition in accordance with the invention.

In a further aspect, the present invention also provides a method of treating skin, hair or nails, comprising topical application of a composition in accordance with the invention.

Considering now the compounds of the invention, R1 is preferably aliphatic and preferably has 10-24 C atoms, more preferably 10-18 C atoms.

Examples of compounds within the scope of the general formula that have been synthesised are shown in Figures 3 to 9.

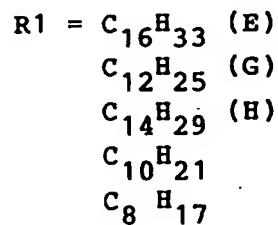
The compound of Figure 3 is referred to herein as pseudoceramide I, and in this compound:



- 7 -

W, Y2 and R7 are absent.

The compounds of Figure 4 include 3 compounds referred to herein as pseudoceramide E, G and H respectively. In these compounds:



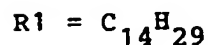
R2-R6, R8-R10 = H

X1, X2 = H

Y1 = OH

W, Y2 and R7 are absent.

In the compound of Figure 5:

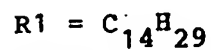


R2-R10 = H

X1, X2 = H

Y1, Y2 = OH

In the compound of Figure 6:



R2-R6 and R8 = H

X1, X2 = H

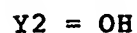
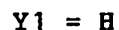
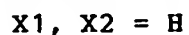
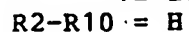
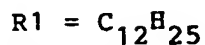
Y1 = OH

W, Y2 and R7 are absent

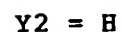
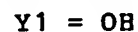
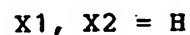
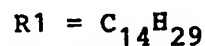
Z, R9 and R10 are absent.

- 8 -

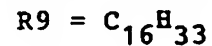
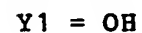
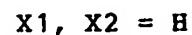
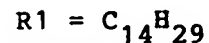
In the compound of Figure 7:



In the compound of Figure 8:



The compound of Figure 9 is referred to herein as compound 10, and in this compound:



The currently preferred compounds for skin treatment purposes are pseudoceramide E and pseudoceramide H.

The compounds are conveniently prepared by treatment of the corresponding alkylaminoalcohol/diol/triol produce a diamide, eg by use of the diester method of the acid chloride method. These are standard methods of amide

- 9 -

preparation well known to those skilled in the art. The relevant alkylaminoalcohol/diol/triol can be prepared using known techniques, eg as described in Bull. Chim. Soc. Fr. (1943), 10, 347.

In another aspect, the invention thus provides a method of preparing a compound in accordance with the invention, comprising treating an alkylaminoalcohol/diol/triol to produce the corresponding diamide.

Brief description of the Figures

Figure 1 shows the formula of ceramide;

Figure 2 shows the general formula of compounds in accordance with the invention; and

Figures 3 to 9 show the formulae of particular compounds in accordance with the invention.

The invention will be further explained, by way of illustration, in the following examples.

Example 1

Pseudoceramide H (also known by the Trade Name Questamide H), the formula of which is shown in Figure 4, was prepared as follows:

N-hexadecyl-2-aminoethanol was prepared by the method described in Bull. Chim. Soc. Fr. (1943), 10, 347.

The corresponding diamide was produced by the diester method, as follows.

- 10 -

N-Hexadecyl-2-aminoethanol (0.06mol) and cyclohexane (300ml) were charged to a 500ml reaction flask fitted with dropping funnel, overhead stirrer and Dean-Stark apparatus with condenser. The mixture was heated with stirring to reflux, and dimethyl malonate (0.03mol) was added over 10 minutes. The stirring/heating was continued until no more methanol appeared. The reaction mixture was cooled and filtered to give the diamide (13.2g, 69% yield).

In combination with other intercellular lipids such as cholesterol and fatty acids, Pseudoceramide H forms "structured" liquid crystals similar to those formed by natural ceramide. Pseudoceramide H also forms a gel-like structure with squalene in a similar way to natural ceramide.

Example 2

Compound 10, The formula of which is shown in Figure 9, was prepared as follows:

N-2-hydroxyethylcetylamine (20g, 0.070mol), dimethyl

- 11 -

hexadecylmalonate (13.5g, 0.035mol) and cyclohexane (100ml) were charged to a 250ml reaction flask equipped with a Dean-Stark take off. The mixture was stirred with heating to reflux for 190hrs. The solvent was removed in vacuo, leaving an off-white solid residue. This was recrystallised from dichloromethane, and dried to give compound 10, m.pt. 50-51°C. IR and NMR spectra support the structure as shown in Figure 9.

Example 3

A cosmetic skin cream composition, particularly suited to use on dry skin, was made from the following ingredients:

<u>CTFA NAME</u>	<u>INGREDIENTS</u>	<u>wt%</u>
<u>Phase A</u>		
Carbomer	Carbopol 940	0.34
Propylene glycol		3.45
Methyldibromo glutaronitrile		
and phenoxyethanol	Euxyl K400	0.10
Triethanolamine		1.62
Deionised water		to 100.00

Phase B

Cetareth-25	Cremaphor A25	1.30
Glyceryl stearate and PEG-100		
Stearate	Arlacel 165	3.25
Stearic acid		1.30
Isopropyl myristate	Estol IPM	5.00
Capric/caprylic triglyceride	Estol GTCC	7.00
Propylene glycol dicaprylate/ dicaprates	Estol PDCC	4.00
Soy sterol	Generol 122	0.50
Myristic acid		0.50
Hydroxycetamide	Questamide H	1.00
Fragrance	Quest	0.20

Hydroxycetamide is the proposed CTFA name of Questamide H (or pseudoceramide H).

The carbomer was mixed and dispersed in water, and the remaining ingredients of phase A added. The ingredients of phase B were mixed. Phase A and Phase B were both heated to 80°C. Phase B was added to phase A with shearing. Once a homogeneous mixture had been produced the mixture was stirred until cool.

This produced a homogeneous cream of pH 7.5 suitable for topical application to the skin as appropriate.

Example 4

A cosmetic skin cream composition was made from the following ingredients:

<u>CFTA NAME</u>	<u>TRADE NAME</u>	<u>%W/W</u>
<u>Phase A</u>		
Carbomer	Carbopol 980	0.20
Propylene Glycol		3.45
Triethanolamine		0.20
Deionised Water		to 100.00
<u>Phase B</u>		
Ceteareth-6 Stearyl Alcohol	Cremaphor A6	1.00
Ceteareth-25	Cremaphor A25	1.00
Stearic acid		0.80
Capric/caprylic triglyceride	Miglyol 812	4.25
Dimethicone	Silicone 200/350	0.80
Cetyl alcohol		0.80
Mineral oil		2.00
Soy Sterol	Generol 122	0.60
Hydroxycetamide	Questamide H	0.80
<u>Phase C</u>		
Methyldibromo Glutaronitrile	Euxyl K400	0.10
and Phenpoxyethanol		
Fragrance	Quest	0.20

The ingredients of phase A were mixed with shearing. The

- 14 -

ingredients of phase B were mixed. Phase A and phase B were both separately heated to 80°C. Phase B was slowly added to phase A with shearing. The mixture was cooled to 45°C. The ingredients of phase C were mixed together, and then added to the cooled mixture of phases A and B (at 45°C), and stirred until cool.

This produced a homogeneous light, white cream of pH 6.3 suitable for topical application to the skin.

Example 5

A cosmetic skin cream composition was made from the following ingredients:

<u>CFTA NAME</u>	<u>TRADE NAME</u>	<u>%W/W</u>
<u>Phase A</u>		
Carbomer	Carbopol 940	0.22
Propylene Glycol		4.00
Methylparaben	Nipagin M	0.20
Deionised Water		to 100.00
<u>Phase B</u>		
Squalene	Prisorine SQV	6.50
Mineral Oil		3.00
Cetyl Alcohol		0.50
Glyceryl Stearate (NSE)	Estol	3.25
Dimethicone	DC 200/350	0.80
Lanolin Alcohol	Super Hartolan	1.00
Glyceryl Stearate (and)	Lexemul 561	3.25
PEG-100 Stearate		
Propylparaben		0.10

- 15 -

Proprietary Emulsifying Wax	Polawax	3.25
Isopropyl Myristate	Estol IPM	3.10
Myristic Acid		0.25
Soy Sterol	Generol 122	0.35
Octyl Palmitate	Estol EHP	4.00
Hydroxycetamide	Questamide H	2.00

Phase C

Triethanolamine		0.38
Deionised Water		1.00
Fragrance	Quest	0.25

Phase D

Imidazolidinyl Urea	Germall 115	0.20
Deionised Water		3.00

The ingredients of phase A were mixed with shearing. The ingredients of phase B were mixed. Phase A and phase B were both separately heated to 80°C. Phase B was slowly added to phase A with shearing. The mixture was cooled to 45°C. The ingredients of phase C were then added individually to the cooled mixture of phases A and B (at 45°C). The ingredients of phase D were mixed and added to the mixture of phases A, B and C, and stirred until cool.

This produced a homogeneous rich bodied, glossy cream of pH 5.8 suitable for topical application to the skin.

Example 6

Oil in water emulsions were made from the following ingredients:

- 16 -

		wt%	
<u>CFTA NAME</u>	<u>TRADE NAME</u>	<u>Batch' 1</u>	<u>Batch 2</u>
<u>Phase A</u>			
Water		to 100.00	to 100.00
Methyl paraben	Nipagin M	0.20	0.20
Polyacrylamide	Sepigel 305	1.00	1.00
(&) C13-14			
Iso paraffin (&) Laureth 7			
<u>Phase B</u>			
Cetyl Alcohol		3.00	3.00
Squalene		2.84	2.84
Propyl paraben	Nipasol M	0.15	0.15
Pentaerythritol tetra			
caprate-caprylate	Crodamol PTC	2.83	2.83
Diisoarachidyl			
Dilinoleate	Liquiwax DIEFA	2.83	2.83
Ceteareth-20	Empilan KM20	3.00	3.00
Dimethicone	Silicone	0.50	0.50
	200/350		
Hydroxycetamide	Questamide H	-	2.00
<u>Phase C</u>			
Water		2.00	2.00
Imidazolidinyl Urea	Germal 115	0.15	0.15
	pH	6.80	6.80

The emulsions were made by stirring the Sepigel 305 into

- 17 -

cold water of phase A until it was dispersed. The remaining ingredients of phase A were then added. The ingredients of phase B were mixed. Phase A and phase B were both heated to 80°C. Phase B was added to phase A whilst shearing. Once a homogenous mixture had been produced the mixture was stirred until cool. The ingredients of phase C were mixed together, added to the cooled mixture of phases A and B and further mixed.

The viscosity of batches 1 and 2 was tested on a Viscometers UK machine, model ERV-8, using the heliopathe, and results were as follows:

	<u>Batch 1</u>	<u>Batch 2</u>
T-Bar	B	B
Speed	10	10
CPS	2080	18160

These show that batch 2, which includes 2.00% pseudoceramide H, has a much higher viscosity than batch 1, which does not include pseudoceramide H.

Example 7

Oil in water emulsions were made from the following ingredients:

<u>CFTA NAME</u>	<u>TRADE NAME</u>	<u>Batch 1</u>	<u>Batch 2</u>
<u>Phase A</u>			
Water		to 100.00	to 100.00
Methyl paraben	Nipagin M	0.20	0.20

- 18 -

Phase B

Avocado Oil		2.00	2.00
Isopropyl myristate		7.00	7.00
Cetyl alcohol		0.50	0.50
Ceteareth-20	Empilan KM20	1.00	1.00
Dimethicone	Silicone 200/350	1.00	1.00
Propyl paraben	Nipasol M	0.10	0.10
Hydroxycetamide	Questamide H	-	2.00

Phase C

Water		2.00	2.00
Imidazolidinyl Urea	Germal 115	0.15	0.15
	pH	7.40	7.10

The emulsions were made by separately mixing the ingredients of phases A and B and heating the 2 mixures to 70°C. Phase B was added to phase A whilst shearing. Once a homogenous mixture had been produced the mixture was stirred until cool.

The viscosity of batches 1 and 2 was tested on a Viscometers UK machine, model ERV-8, and results were as follows:

	<u>Batch 1</u>	<u>Batch 2</u>
Spindle	R3	R3
Speed	10	10
CPS	30	7230

- 19 -

These show that batch 2, which includes 2.00% pseudoceramide H, has a much higher viscosity than batch 1, which does not include pseudoceramide H.

Claims

1. A compound of the formula shown in Figure 2 in which:
R1 is a hydrocarbon group;
R2-R8 are each independently H or CH₃;
R9 and R10 are each independently H or a hydrocarbon group of up to 24 C atoms;
X1 and X2, are independently H or OH;
Y1 and Y2 are H or OH, at least one of Y1 and Y2 being OH;
wherein the C atom Z, with associated R9 and R10, can be absent; and
the C atoms W, with associated R7 and Y2, can be absent.
2. A compound according to claim 1, wherein R1 is aliphatic and preferably has 10 to 24 C atoms, more preferably 16 to 18 C atoms.
3. A compound according to claim 1 or 2, comprising a structure shown in Figure 4.
4. A composition, particularly a cosmetic composition, suitable for topical application to skin, hair or nails, comprising a compound in accordance with any one of claims 1 to 3.
5. A composition according to claim 4, including one or more compounds in accordance with claim 1, 2 or 3, in an amount in the range 0.0001 to 50% by weight, preferably 0.001 to 20% by weight, more preferably 0.1 to 10% by

- 21 -

weight.

6. A composition according to claim 4 or 5, including a suitable carrier vehicle for the compound.

7. A closed container containing a composition in accordance with any one of claims 4, 5 or 6.

8. Use of a compound in accordance with claim 1, 2 or 3 as an agent for skin water barrier repair, for improving nails and/or for improving hair.

9. A method of treating skin, hair or nails, comprising topical application of a composition in accordance with any one of claims 4, 5 or 6.

10. A method of preparing a compound in accordance with claim 1, 2 or 3, comprising treating an alkylaminoalcohol/diol/triol to produce the corresponding diamide.

1/3

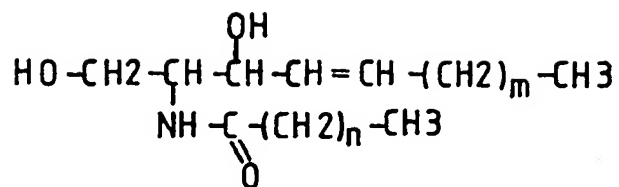


Fig. 1

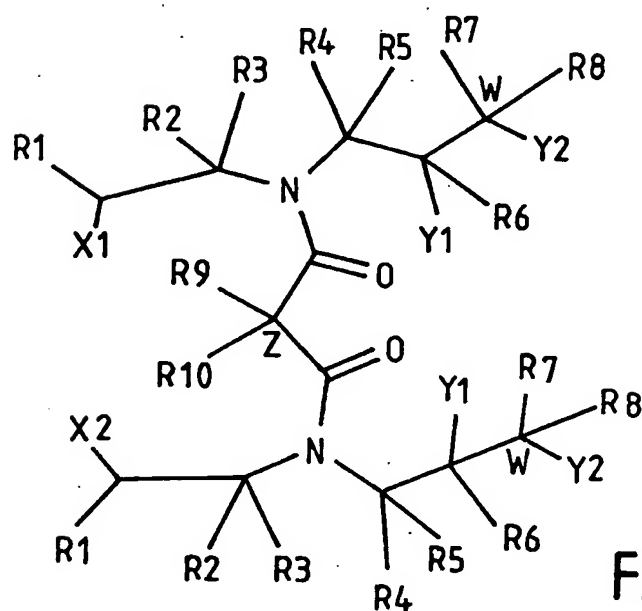


Fig. 2

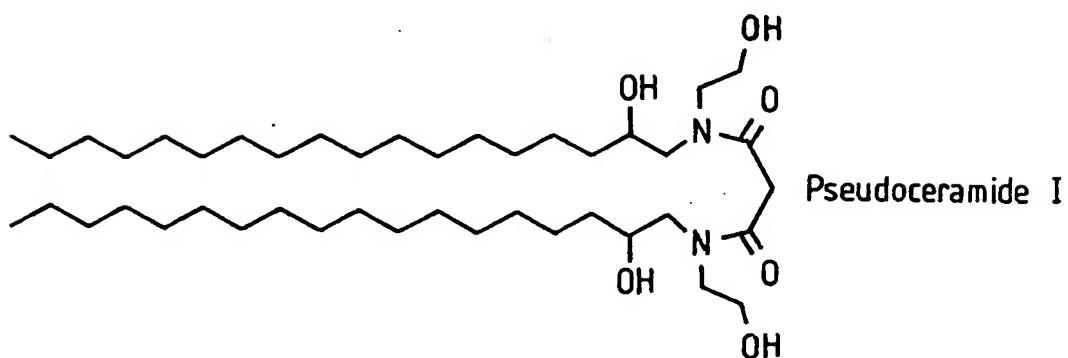


Fig. 3

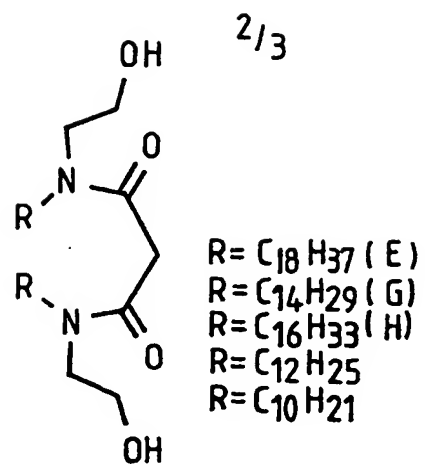


Fig. 4

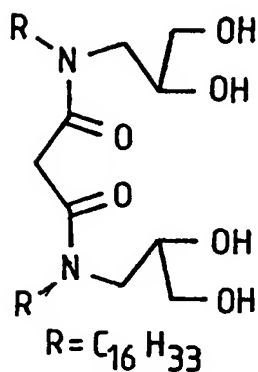


Fig. 5

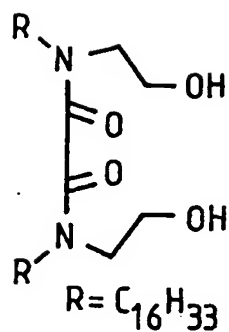


Fig. 6

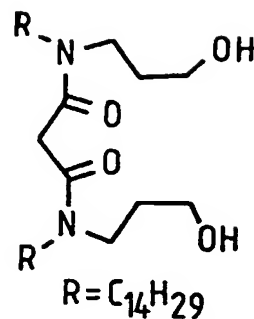


Fig. 7

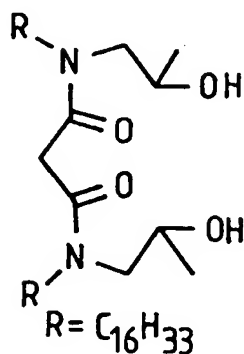


Fig. 8

3/3

Compound 10

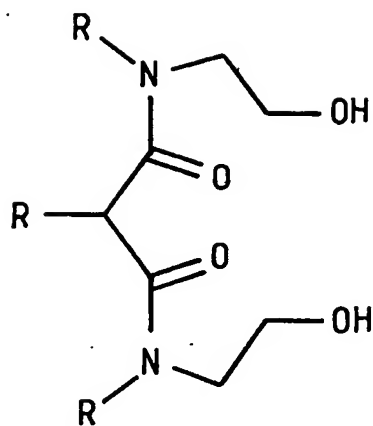
 $10 : R = n\text{-C}_{16}\text{H}_{33}$

Fig. 9

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/GB 93/02061

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C233/18 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,A,26 04 554 (HENKEL UND CIE. G.M.B.H.) 11 August 1977	1
Y	see claims see page 8; example A see page 9 - page 10; example B7	2-10
A	JAOCS, J. AM. OIL CHEM. SOC., 65(5), 820-5 1988 MICICH, T. J. ET AL. 'Wetting properties of nonionics from branched fatty diamides' see page 822, left column, paragraph 2 see page 822; table 1	1
A	EP,A,0 450 527 (KAO CORPORATION) 9 October 1991 see claims	1-10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

14 December 1993

Date of mailing of the international search report

29. 12. 93

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Authorized officer

Pauwels, G

INTERNATIONAL SEARCH REPORT

Intern. Appl. No.
PCT/GB 93/02061

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 482 860 (UNILEVER NV.) 29 April 1992 cited in the application see claims	1-10
Y	EP,A,0 420 722 (L'ORÉAL) 3 April 1991 cited in the application see claims	2-10

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter. Application No

PCT/GB 93/02061

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EP-A-0420722	03-04-91	FR-A- 2652002 CA-A- 2025790 JP-A- 3193754 US-A- 5149860 US-A- 5198470	22-03-91 22-03-91 23-08-91 22-09-92 30-03-93